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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,386	12/13/2005	Hidekazu Inoue	58778.000005	8779

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EXAMINER	
MOORE, SUSANNA	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/560,386	INOUE ET AL.	
	Examiner	Art Unit	
	Susanna Moore	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12-13-05, 3-6-2006.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Objections

1. Claim 1 is objected to because of the following informalities: Markush claims should be written in the alternative. Appropriate correction is required.

2. Claim 5 is objected to because of the following informalities: the word ----to--- needs to be inserted between the words "according" and "claim". Appropriate correction is required.

3. Claim 8 is objected to because of the following informalities: the word ---the--- needs to be inserted between the words "as" and "active". Appropriate correction is required.

Claim Rejections – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant cannot define a group, e.g. R5 and R6, with the same

variables as R5 and R6. In other words, the groups "R5 and R6" can not be substituted with a "NR5R6" substitution. These substitutions could go on endlessly.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 23, the term "PDE7" renders the claim indefinite because it is unclear what Applicant regards as the invention. "PDE7" is found in various isoforms: PDE7A1, PDE7A2, PDE7A3 and PDE7B. There is no PDE7 per se. Does Applicant intend all or just some, and in the latter case, which one(s)?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the Specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims 1-9 are drawn to solvates. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton*

International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows: Claims 1-9 are drawn to compounds of formula (IA) and (IB), compositions thereof, methods of use and methods of treatment as PDE7 inhibitors.

(A) Breadth of claims.

(a) Scope of the compounds. The instant claim embraces hundreds of thousands of compounds with a substituted phenyl or pyridyl pyrazolopyrimidinone scaffold with a variety of substituents at four positions. These variations to the pyrazolopyrimidinone scaffold give a diverse range of compounds, which provide different physical and chemical properties to the individual substituted pyrazolopyrimidinone framework.

(b) Scope of the enzymes covered. Two genes, PDE7A and PDE7B, have been identified that encode PDE7. Three different isoforms of PDE7A have been isolated and identified: PDE7A1, PDE7A2 and PDE7A3. Another gene family member is PDE7B, with approximately 70% homology.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information, 0.1 to 100 mg, is broad. Moreover, this is generic, the same for the many disorders covered by the Specification and all PDE7 isoforms. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for inflammatory disease or an immunological disease.

(D) State of the Prior Art: These compounds are substituted phenyl or pyridyl pyrazolopyrimidinone compounds. So far as the examiner is aware, no substituted phenyl or pyridyl pyrazolopyrimidinone compounds of any kind have been used for the treatment of any or all inflammatory diseases and immunological diseases nor is there any useful inhibition of these isoforms per se. The state of the clinical arts in therapeutic diseases is such that as of 2005, there were no therapeutic uses for inhibiting PDE7. An articled titled, "PDE7 Inhibitors," (Expert. Opin. Ther. Patents, 2002, 12(4), 601-603) recites "...PDE7 inhibitors may be useful in the treatment of asthma and allergic diseases...". While the article mentions a therapeutic potential of PDE7 inhibitors for the treatment of asthma and allergic diseases, it is only suggestive of a utility for PDE7 inhibitors. Thus, the use is just a possibility. In fact, Beavo et. al. (Science, 1999, 283, 848-850), only "suggests that PDE7 may be a good target for selective therapeutic modulation of T cell responsiveness." Here again, the article only raises this one possibility. Lastly, Castro et. al. (Med. Res. Rev., 2005, 25(2), 229-244) states "PDE7 has the potential to regulate human T cell functions...However, its specific role in T cell function is still unclear...". Their potential remains at the level of speculation. As of the filing date, there are no references, which provide firm evidence that inhibition per se of PDE7 isoforms is of any established use.

(E) Working Examples: The Applicant has not provided any working examples to any utility. Applicant presents summarized data for approximately 200 compounds as inhibition of an unspecified PDE7 isoform on page 52-56 of the Specification. Moreover, of the different isoforms currently known for PDE7, i.e. PDEA1, PDEA2, PDEA3 and PDEB, the inhibition assays do not discriminate as to which isoform, if any one, was used for the assay.

(F) Skill of those in the art: The claim(s) contains subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled. Even after the filing date of this case, research shows only the possibility of treating inflammation with a PDE7 inhibitor. Castro et. al. (Med. Res. Rev., 2005, 25(2), 229-244) states "PDE7 has the potential to regulate human T cell functions...However, its specific role in T cell function is still unclear...". As of 2005, there are no references, which provide conclusive evidence that the method of use or method of treatment is enabled for PDE7 inhibitors.

(G) The quantity of experimentation needed: Owing especially to factors A, C and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. ***In re Wright*****, 999**

F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunnage et. al. (U.S. 6,677,335 and U.S. 6,407,114).

The current invention teaches substituted pyrazolopyrimidinones of formula (IA) or (IB) for the inhibition of PDE7 wherein R1= t-butyl or cyclohexyl, R2= methyl, R3= SO_2N- forming a piperazine ring substituted at the para position of the pyridine ring and R4= ethoxy group. The instant claims are drawn to both compounds and compositions.

Bunnage et. al. (U.S. 6,677,335) teaches several substituted pyrazolopyrimidinones for treating erectile dysfunction (ED), which include generically instant compounds of structure (IB). See column 2, structure (I). The definition of the various variable groups include: R1= cyclohexyl, R2= ethyl, R3= substituted at the 5 position of the pyridine ring with an SO2N- piperazine ring and R4= ethoxy. See the species shown in column 92, example 82. The claims are drawn to both compounds and formulations as per claim 8.

Bunnage differs from the instant claims in the following manner: A) the substitution of the pyrazolo ring in that the instant claim is substituted at the N-1 position while the prior art reference is substituted at the at the N-2 and B) the substitution on the pyridine ring of the sulfonamide derivative is a the 5-position versus Applicant's 4-position.

A. The difference between a substituent at the N-1 position versus the N-2 position on the pyrazolo ring is that of positional isomers. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties.

B. Bunnage also differs from the instant claim in the substitution on the phenyl ring of the sulfonamide derivative, the 5-position versus Applicant's 4-position substitution. Here again, the isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt,* 208 USPQ 343, 349; *In re Mehta,* 146 USPQ 284, 287; *In re Surrey,* 138 USPQ 67; *Ex Parte Ullyot,* 103 USPQ 185; *In re Norris,* 84 USPQ 459; *Ex Parte Naito,* 168 USPQ 437, 439; *Ex parte Allais,* 152 USPQ 66; *In re Wilder,* 166 USPQ 545, 548; *Ex parte Henkel,* 130 USPQ 474; *Ex parte Biel,* 124 USPQ 109; *In re Petrzilka,* 165 USPQ 327; *In re Crownse,* 150 USPQ 554; *In re Fouche,* 169 USPQ 431; *Ex parte Ruddy,* 121 USPQ 427; *In re Wiechert,* 152 USPQ 249, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (Englehardt) and "Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original). Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Position isomers are the basic form of close "structural isomers." Similar is *In re*

Schechter and LaForge, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds ... a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para)." See also MPEP 2144.09, second paragraph.

Bunnage et. al. (U.S. 6,407,114) teaches several substituted pyrazolopyrimidinones for inhibiting cGMP PDE5, which include generically instant compounds of structure (IA). See column 1, formula (IA). The generic definition of the various variable groups include: R1= lower alkyl, R2= lower alkyl, R3= ethoxy and R4= substituted at the 5 position of the pyridine ring with an SO2-piperazine-4-ethyl.

Bunnage et. al. teaches that the ethyl substituents can be placed at both the R1 position and R3 position of the pyrazolo ring. See examples 25 and 43 mentioned above.

Example 55, in column 33, provides a compound where R1= ethyl, R2= pyrazinyl, R3= ethoxy and R4= substituted at the 5 position of the pyridine ring with an SO2-piperazine. Example 25, column 43, provides a compound where R1=cyclopentyl, R2= ethyl, R3= ethoxy and R4= substituted at the 5 position of the pyridine ring with an SO2-piperazine-4-ethyl.

Bunnage differs from the instant claims in the substitution of the pyrazolo ring in that the instant claim is substituted at the N-1 position while the reference is substituted at the at the N-2

position. Bunnage also differs from the instant claim in the substitution on the pyridine ring of the sulfonamide derivative. All said replacements are positional isomers and as a result, can be explained with the same argument mentioned above. The claims are drawn to both compounds and formulations as per claim 8.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims in U.S Patent 6,677,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims are also embraced in U.S Patent 6,677,335.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The compounds in the present case represented by formula (IA) and (IB) form positional isomers of the compounds in copending case 10/866,198 represented by formula (IA) and (IB), wherein A= N. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify for reasons set forth above.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SM

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